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Meta-Analysis

The risk of Parkinson's disease in inflammatory bowel disease: A systematic review and meta-analysis

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ABSTRACT

Background: Several studies have reported an increased prevalence of Parkinson disease (PD) amongst patients with inflammatory bowel disease (IBD) with conflicting results. We aimed to evaluate the risk of PD in the IBD population by conducting a meta-analysis (MA).

Methods: A systematic review with MA of the existing literature was conducted. The main outcome of interest was the incidence of developing PD in patients previously diagnosed with IBD.

Results: Four studies were included in this MA. The overall risk of PD in IBD was significantly higher than controls (RR 1.41, 95% c.i. 1.19–1.66). Crohn's disease had a 28% increased risk of PD and ulcerative colitis had a 30% increased risk of PD compared to controls (CD: RR 1.28, 95% c.i. 1.08–1.52, UC: RR 1.30, 95% c.i. 1.15–1.47).

Conclusion: The MA detected an increased risk of PD in the IBD population and CD/UC subgroup. These results merit further clinical validation in future studies.

1. Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract with unknown etiology. The major IBDs include Crohn's disease (CD) and ulcerative colitis (UC) [1]. It is well established that IBD involves aberrant immune activity, triggering subsequent host inflammatory responses. This is a fundamental element in the pathogenesis of neurodegenerative disorders since the central and enteric nervous system are inherently linked, also known as the gut-brain axis [2].

PD and IBD are chronic disorders that share similar inflammatory activities implicated in disease pathogenesis. Various cytokines including interleukin-1β and tumor necrosis factor-α have been shown to be linked with PD and IBD [3,4]. Additionally, the spectrum of cytokines observed in the striatum and substantia nigra pars compacta of patients with PD and of PD animal models [5,6] is remarkably identical to those observed in patients with IBD [4,7].

Lewy bodies are neuronal α-synuclein inclusions and a hallmark of PD. The expression of α-synuclein-associated intestinal inflammation has been linked to norovirus infections in children [8]. LRRK2 (leucine-rich repeat kinase 2), which regulates the induction of autophagy, is known to increase the risk of PD [9]. Recently, Hui et al. [10] reported that CD and PD shared LRRK2 alleles, shedding light on the pathogenesis of these two seemingly unrelated diseases.

Based on the association between PD and IBD, population-based studies were performed to investigate the co-occurrence of PD in the IBD background. A general increase in the hazard ratio was detected [11–14]. However, another case-control study demonstrated conflicting results by indicating an inverse association between PD and IBD [15]. More specifically, the association between CD or UC as a separate entity and PD remains controversial according to current literature [13,14]. Therefore, this MA aimed to systematically evaluate the risk of PD in the IBD population.

2. Methods

2.1. Search strategy

Using PubMed and Embase databases, an extensive search was conducted by two independent reviewers (ZF AND LCL) employing the following search strategy: "Idiopathic Parkinson's Disease", "Lewy Body Parkinson Disease", "Lewy Body Parkinson's Disease", "Primary Parkinsonism", "Parkinsonism", "Primary", "Parkinson Disease", "Idiopathic", "Parkinson's Disease", "Parkinson's Disease, Idiopathic", "Parkinson's Disease, Lewy Body", "Idiopathic Parkin-

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son Disease", "Paralysis Agitans and Inflammatory Bowel Disease", "Bowel Diseases, Inflammatory", "Crohn's disease" and "ulcerative colitis". All terms were searched as key words and MeSH headings where available. Search results were screened for potentially relevant studies by title and abstract; followed by full-text review of shortlisted publications. The references of relevant publications such as reviews were further searched and manually cross-referenced for additional suitable publications. The inclusion criteria were: (1) cohort or case-control studies including patients with a diagnosis of IBD; CD and/or UC; (2) studies using PD as a primary outcome during follow-up; (3) published in full form in peer-reviewed literature. Inter-observer discrepancy occurred amongst 4 (2.3%) publications.

2.2. Data extraction

Data was extracted by two independent reviewers with corroboration by two senior reviewers (GJF and ZWM). Discrepancies were resolved by consensus and involvement of senior reviewers. The corresponding author of the relevant article was contacted via e-mail if additional data was required for analysis.

2.3. Outcome measures

The main outcome measure was the occurrence of PD during follow up, the estimated risk of PD in IBD, CD and UC respectively using time since index dates as the underlying time scale.

2.4. Quality assessment

To assess the study quality, an evaluation system based on the Newcastle–Ottawa Scale was adopted (range 0–9 stars) [16]. The included studies were judged on 3 aspects: the selection of study populations, the comparability of the populations, and determination of exposure (case-control studies) or outcomes of interest (cohort studies), respectively. The full score was 9 stars, and a high-quality study was defined as >seven stars. The rankings for each study are shown in Table S1.

2.5. Statistical analysis

The association between PD and IBD was expressed as risk ratios (RRs) with 95% confidence intervals (95% CI), which represents the relative risk of developing PD for IBD patients compared to controls. Pooled RRs were calculated using the random effects model, which was used to account for variations between studies and provide a more conservative pooled estimate. Heterogeneity across the studies was assessed using the I^2 statistic, while $I^2 > 50\%$ was considered to indicate significant heterogeneity across studies. Further subgroup analysis was performed based on the disease subtype (CD vs. UC). Sensitivity analyses was used to test the robustness of our results though the sequential removal single studies, to investigate if a single study was driving the study results. Funnel plots were not obtained due to an insufficient number of included studies.

Statistical analyses was performed using Cochrane's Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre,

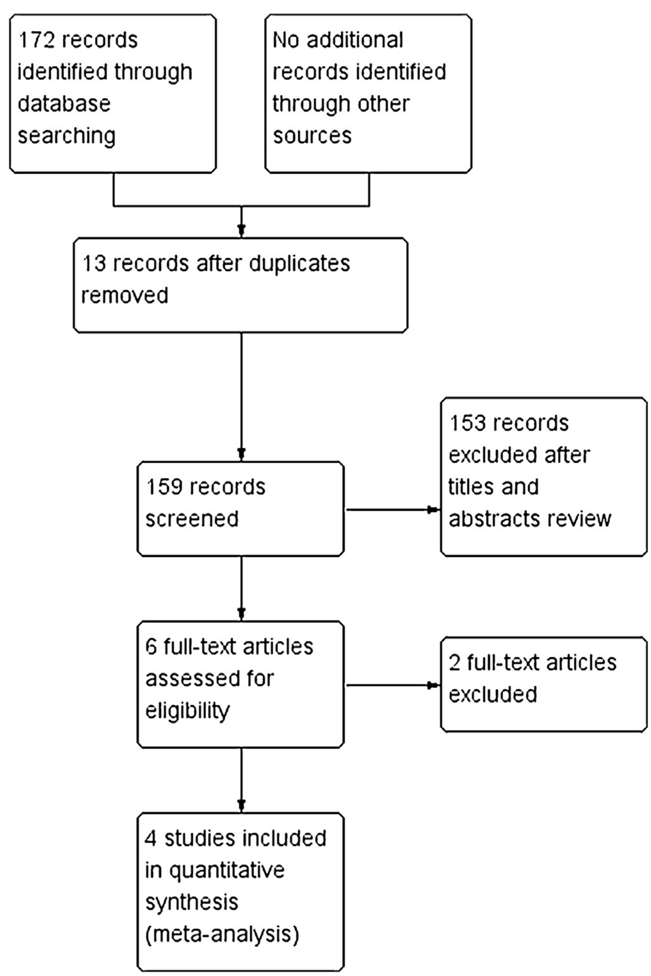

Fig. 1. Flow diagram outlining the study selection process.

Table 1
Characteristics of the included studies.

Author	Country	Year	Study period	IBD patients	Control	Rate[a], IBD/control	Adjustment
Inga Peter	United States	2018	2000–2016	144,018	720,090	0.73/0.57	Time-varying age group, sex, offset by time at risk
Jung-Chun Lin	Taiwan	2016	2000–2011	8373	33,492	1.74/1.21	Age, sex, comorbidities of diabetes, hypertension, hyperlipidemia, stroke, CAD, head injury, depression, CKD.
Petra Weimers	Sweden	2018	2002–2014	39,652	396,520	0.3/0.2	Sex, age, index date, place of residency
Marie Villumsen	Denmark	2018	1977–2014	76,477	7,548,259	0.37/0.22	Charlson Comorbidity Index

CKD: chronic kidney disease, CAD: chronic artery disease.
[a] Incidence rate per 1000 person-years.

The Cochrane Collaboration, 2014). A $p < 0.05$ was considered statistically significant. All statistical tests were two-sided.

3. Results

3.1. Study characteristics

The preliminary search yielded 172 publications from electronic databases using the search algorithm. A total of 166 items were excluded after reviewing the titles and abstracts. Two publications were excluded as they solely reported the incidence of IBD in a PD background. The screening process is shown in Fig. 1. Four publications were finally included in the MA including a total of more than 8.9 million patients. Three were published in 2018 and one in 2016, reporting results from United States, Denmark, Sweden and Taiwan, respectively. All publications studied PD incidence (measured by the rate per 1000 person-years during follow-up) in the general IBD population using Cox regression. Hazard ratio (HR) was used to calculate the PD incidence in all studies. Characteristics of the included studies were summarized in Table 1.

3.2. Quality of studies

The included studies were of consistently reasonable quality with considerably large sample numbers, clearly defined aims and outcomes. However, common limitations to all studies included detection bias, that is, when studying the co-occurrence of two diseases, diagnosis of a single disease may increase the likelihood of concomitant diagnosis of another disease. In addition, potential confounders including smoking status and medication data were unavailable as all included publications were nationwide population-based studies Table 2.

3.3. Overall risk of Parkinson's disease

All studies were pooled to assess the effects of prior IBD diagnosis on PD development. As shown in Fig. 2, IBD was associated with an increased incidence of PD after combining the data of four studies (RR 1.41, 95% CI 1.19–1.66, $p = 0.0001$). Peter et al. [11] and Weimers et al. [12] reported an increased hazard ratio in both CD and UC groups. However, the largest cohort study from Denmark [13], which followed up 76,477 IBD individuals and 7,548,259 controls, showed the risk of parkinsonism was significantly higher among patients with UC (HR = 1.35; 95% CI 1.20–1.52) and did not significantly differ amongst patients with Crohn's disease (HR = 1.12; 95% CI 0.89–1.40). Another cohort study from Taiwan [14] identified an increased risk of PD in patients with Crohn's disease (HR = 1.40; 95% CI 1.11–1.77) but not UC (HR = 0.94; 95% CI 0.49–1.84). Therefore, we conducted subgroup analysis to investigate the effects of CD and UC on PD development, separately. Pooled analysis showed both CD and UC was associated with an increased risk of PD compared to the control group (CD: RR 1.28, 95% CI 1.08–1.52, $p = 0.0002$; UC: RR 1.30, 95% CI 1.15–1.47, $p < 0.0001$). Study heterogeneity was detected whilst analyzing IBD ($I^2 = 83\%$, $p = 0.003$) but not CD ($I^2 = 22\%$, $p = 0.28$) or UC ($I^2 = 0\%$, $p = 0.43$) independently.

Table 2
Summary of meta-analysis results.

Comparison	Study heterogeneity			Risk ratio (95% c.i.)	p Value
	Chi^2	p value	I^2		
IBD vs. control	14.20	0.003	83%	1.41 (1.19–1.66)	<1e−4
CD vs. control	2.56	0.28	22%	1.28 (1.08–1.52)	2e−4
UC vs. control	1.70	0.43	0%	1.30 (1.15–1.47)	<1e−4

CD: Crohn's disease; UC: ulcerative colitis.

3.4. Risk of Parkinson's disease in different subgroups

Two studies had accessible data of PD incidence in age-, sex-specific subgroup [12,13]. Pooled analysis showed IBD patients had an increased risk of PD in male (RR 1.53, 95% c.i. 1.09–2.15, $p = 0.01$) and female subgroup (RR 1.49, 95% c.i. 1.29–1.72, $p < 1e{-4}$). For age-specific subgroup, IBD patients had an increased risk of PD in patients >65 years old (RR 1.32, 95% c.i. 1.16–1.51, $p = 0.0001$) and patients ≤65 years old (RR 1.64, 95% c.i. 1.45–1.96, $p < 0.0001$).

3.5. Sensitivity analysis

To explore the potential effects of any single study on heterogeneity in addition to the outcome, studies were sequentially removed to obtain the RR values. Upon analysis of the remaining studies, similar findings were observed in the overall IBD cohort and CD/UC subgroups, suggesting that no single study drove the pooled RRs for PD risk. However, the removal of Villumsen et al. [13] significantly reduced the study heterogeneity ($I^2 = 0\%$, $p = 0.89$), suggesting this study was a source of heterogeneity. We next compared the results of data pooling between random-effects and fixed-effect models. The use of random- vs fixed-effect models yielded similar RR values (Table S2).

4. Discussion

With consistent genetic and functional connections established between PD and IBD [17–22], various clinical experiments have emerged to investigate the co-occurrence of PD and IBD. The current study conducted a MA across studies to access the risk of PD in IBD populations. Our results suggested IBD patients had an increased risk of developing PD (RR 1.41, 95% c.i. 1.19–1.66, $p = 0.0001$). Moreover, studies revealed conflicting results as to whether CD or UC was associated with PD. This MA showed an increased risk of PD that remained significant when analyzing CD and UC cohorts independently (CD: RR 1.28, 95% CI 1.08–1.52, $p = 0.0002$; UC: RR 1.30, 95% CI 1.15–1.47, $p < 0.0001$).

To our knowledge, this is the first MA to focus on the risk of PD in IBD patients. Despite the small number of studies included, the

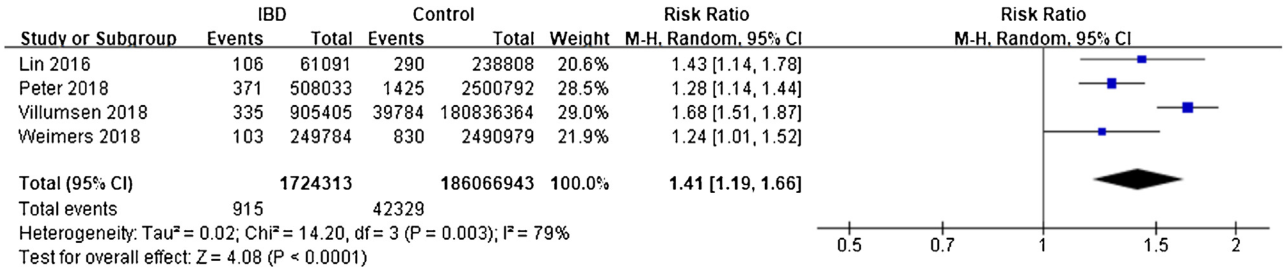

Fig. 2. Forest plot demonstrating the association between the risk of PD and IBD. IBD patients had a 46% increased risk of PD compared to controls. (RR 1.41, 95% CI 1.19–1.66).

patient numbers were large due to the population-based nature of the included studies. In addition, all included studies were cohort studies with a follow-up assessed since the index date of IBD diagnosis and cohort studies may be seen as superior to case-control studies in terms of calculating risk estimates and the prevalence of a specific disease. Therefore, this study is apt to investigate incidence of PD in IBD population.

It is implied from genotyping analysis that the shared defect of LRRK2 alleles is responsible for the co-occurrence of these two diseases [13]. PD is known to be more prevalent amongst senile patients [23] while IBD can develop at any age. Therefore, IBD tends to precede PD during the disease course and most studies investigate PD incidence in IBD patients instead of the other way around. Two studies focusing on IBD incidence among PD patients were not included in this MA [15,24].

The reported incidence rates of PD vary markedly amongst the included studies. This could be partly explained by the different frequency of healthcare use in different countries (surveillance bias), different races of the cohorts, and different clinical diagnostic criteria. In the analysis of age-specific subgroups, patients <65 years old had a more pronounced increase of PD risk compared to those aged $\leq$65 years (64% vs. 32%). This may be caused by the exclusion of a considerable proportion of elderly patients who already developed PD at the time of first IBD diagnosis due to the design of the cohort study.

The heterogeneity of the included studies was small in terms of study design and statistical analysis, suggesting them as suitable for pooled analysis. However, sensitivity analysis showed that the Danish cohort may be a source of heterogeneity when analyzing the studies together. Differences in sample sizes and person-years followed may potentially explain the heterogeneity. Additionally, the risk ratio in this cohort was adjusted for using the Charlon Comorbidity Index whilst other studies either adjusted for specific comorbidity or did not adjust for comorbidity.

The primary strength of this MA was the systematic search for, and assessment of available literature comparing the incidence rates of PD among IBD patients and age-, sex-matched controls. Some studies have accumulated data over time but the results were contradictory, especially when analyzing the risk of PD in CD and UC separately, and therefore a comprehensive review and critical assessment of existing literature was essential to modify healthcare for patients with IBD, Parkinsonism in addition to their family members.

The major limitation of this study was the small number of studies included in the MA, making the article not sufficiently strong to fully justify the final conclusions. However, this could be partly compensated for by the large number of patients. Secondly, publication bias was not considered by obtaining funnel plots due to the insufficient number of studies. Thirdly, none of the included studies presented data concerning smoking status, family history or drug exposure, which are important factors during PD pathogenesis.

In conclusion, this MA identified an increased risk of PD in IBD patients. The increased risk remained significant when separately analyzing CD and UC subgroups. More comprehensive and detailed MA using a larger number of studies are required to validate our findings in the future.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.09.017.

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